claim 26 can be found, *inter alia*, in Example 16. Applicants submit that no new matter is added by the present amendment.

Claims 1-4, 16, 17 and 19-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (1994) Ann. Oncol. 5:S13-S17. The Examiner contends that "[t]he range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in the prior art." (emphasis added.) Applicants respectfully disagree with this contention.

Applicants disagree with the Examiner's characterization of the claimed invention as three apparently unrelated elements: (1) 2-100 mg of anti-Tac antibody; (2) 5-15 mCi ^{90}Y-labeled anti-Tac antibody; (3) 25-75% saturation of total IL-2 receptors. In fact, the claimed invention teaches administering to a patient a specific ratio of conjugated to unconjugated anti-Tac such that 25-75% of the IL-2 receptors are saturated.

The instant specification sets forth a specific algorithm for calculating a proper ratio of conjugated to unconjugated anti-Tac based on a patient's total soluble IL-R levels. The following examples illustrate the importance of this ratio relative to total soluble IL-2R levels. In one example, if a patient with a high soluble serum IL-2R levels such as 75,000 units/ml, is treated with a total of 2 mg anti-Tac conjugate containing from 5-15 2Ci ^{90}Y, the administered radiolabeled antibodies would form complexes with circulating sIL-2R and not

be available for binding to the target tumor cells because less than 25% of IL-2 receptors would be saturated. In this scenario, most of the radiation is delivered to healthy normal tissues. (The amount of radioactivity, i.e., 5-15 mCi, does not affect the amount of radiation-delivering antibodies delivered to the target cells.) According to the claimed invention, as outlined in Example 16, a patient with a sIL-2R level above 50,000 units/ml should receive 20 mg of anti-Tac which is a dose "estimated to yield binding of radiolableled anti-Tac to all circulating Tac-expressing tumor cells and to produce approximately 25 to 75% saturation of the IL-2 receptors" (page 52 of the instant specification). When the patient with high sIL-2R levels is treated with low levels of anti-Tac, the IL-2 receptors are not 25 to 75% saturated and cytotoxic anti-Tac conjugate is not efficiently delivered to the target cells.

Another example that lies outside the claims of the instant invention is a patient having low soluble serum IL-2R levels, such as 1,000 units/ml, and is treated with a high amount of conjugate, for example 20 mg anti-Tac conjugate containing from 5-15 mCi ^{90}Y. While this patient would have saturation of tumor cell surface receptor sites, much of the radiolabeled antibody would remain in the plasma and other extracellular body fluids unbound to tumor cells and therefore delivering radiation to healthy normal tissues. According to the algorithm in Example 16, a patient with sIL-2R levels under 2,000 units/ml should receive 2 mg of anti-Tac per dose which would result in 25 to 75% saturation of IL-2 receptors. Because this patient is not treated according to the claimed invention more than

75% of IL-2 receptors would be saturated and therefore receive sub-optimal treatment. In these examples, the amount of radiation, i.e. 5-15 mCi ^{90}Y, administered does not affect the percentage of antibodies being delivered to the target tumor cells and therefore, knowledge of this parameter alone is insufficient to determine the proper effective dosage for human treatment.

Applicants respectfully disagree with the Examiner's contention that it would have been obvious to "conduct bioavailability analysis to achieve saturation of IL-2 receptors to overcome the effect of soluble IL-2R without diluting antibody specific activity." The Examiner has provided no basis for this contention. It is improper for the Examiner to make obviousness determinations without providing some authoritative support as required by 37 C.F.R. § 1.107(a). However, if the Examiner's statement is based upon his personal knowledge, applicants request the Examiner submit an appropriate affidavit as required by 37 C.F.R. 1.107(b).

As pointed out above, high specific activity was a problem in the prior art that caused cytotoxic agents to be delivered almost exclusively to healthy normal cells. Example 9 shows that the bioavailable fraction of the indium-labeled anti-Tac increased markedly when the quantity of anti-Tac administered in association with the radiolabeled antibody was increased from 1 mg to 50 mg/patient. Simply diluting an anti-Tac conjugate is insufficient to practice the claimed invention. Rather, a specific ratio based upon soluble IL-2R levels must be determined for the claimed invention to be practiced.

Waldmann (Ann. Oncol.) discloses humanized monoclonal antibody-cytotoxic agent conjugates and humanized monoclonal antibodies armed with radionuclides. The amount of radioactivity administered to patients was μCi ^{212}Bi or 5-15 mCi ^{90}Y. Patients in limited clinical trials showed promising results when treated with the conjugates. What Waldmann (Ann. Oncol.) fails to teach or suggest is (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Therefore, applicants assert that there is no teaching or suggestion in Waldmann (Ann. Oncol.) that discloses the claimed invention.

Applicants assert that there is no teaching or suggestion in Waldmann (Ann. Oncol.) for the Examiner to make the determination that the claimed invention "surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in the prior art." The Examiners use of the phrase "surely would have been encompassed" indicates to applicants that even the Examiner could find no such teaching or suggestion in Waldmann (Ann. Oncol.) or any of the other cited prior art. Applicants point out that the claims are not drawn to simply ^{90}Y-labeled anti-Tac but rather to methods of treating disease using a ratio of conjugated to unconjugated anti-Tac antibodies such that 25-75% of IL-2 receptors are saturated. As the Examiner well knows, an anticipatory reference must provide an exact disclosure of the claimed invention. Waldmann (Ann. Oncol.) fails to meet this standard. Waldmann (Ann. Oncol.) does not teach or suggest (a) what doses of

cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Waldmann (Ann. Oncol.) does not teach or suggest the use of an anti-Tac conjugate with the specific activity or specific doses claimed and as such does not anticipate or render obvious the claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the § 102 and § 103 rejections. Claims 1-14, 16, 17 and 19-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (1994) Imp. Adv. Oncol. pp. 131-141. Applicants respectfully disagree with this rejection since there is no additional teaching or suggestion in Waldmann (Imp. Adv. Oncol.) relevant to the claimed invention not already found in Waldmann (Ann. Oncol.).

Waldmann (Imp. Adv. Oncol.) discloses bifunctional antibodies: antibodies conjugated to immunotoxins and to radionuclides. The amount of radiation delivered to patients was 0.5 μCi ^{212}Bi or 5-15 mCi ^{90}Y. Patients receiving the conjugates in limited clinical trials showed promising results. What Waldmann (Imp. Adv. Oncol.) does not teach or suggest is (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Waldmann (Imp. Adv. Oncol.) does not teach or suggest the use of an anti-Tac conjugate with the specific activity or specific doses claimed and as such does not anticipate or render obvious the claimed invention. Applicants

therefore respectfully request reconsideration and withdrawal of the § 102 and § 103 rejections.

Claims 1-14, 16, 17 and 19-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (1993) Leukemia 7:S151-S156. Applicants respectfully disagree with this rejection since there is no additional teaching or suggestion in Waldmann (Leukemia) relevant to the claimed invention not already found in Waldmann (Ann. Oncol.) and Waldmann (Imp. Adv. Oncol.).

Waldmann (Leukemia) discloses humanized anti-Tac conjugated to either cytotoxic agents or radionuclides. The amount of radioactivity in the radionuclide conjugates was 0.5 μCi ^{212}Bi or 5-15 mCi ^{90}Y. Patients treated with the radionuclide conjugates showed promising results in limited clinical trials. What Waldmann (Leukemia) does not teach or suggest is (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment.

Applicants further disagree with the Examiner's assertion that "the prior art teachings of these Waldmann references [Ann. Oncol., Imp. Adv. Oncol. and Leukemia] clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitation." The claimed invention is not taught or suggested in these Waldmann references. The claims of the instant invention are drawn to a method of

treatment using a specific ratio of conjugated to unconjugated anti-Tac producing a saturation level of 25-75% of the IL-2 receptors. This ratio provides the proper dosage for patient administration and is not taught or suggested in any of the cited Waldmann references. These references fail to teach or suggest the use of an anti-Tac conjugate with the specific activity or specific doses claimed. Therefore, the references do not anticipate or render obvious the claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the § 102 and § 103 rejections.

Claims 1-14 and 16-25 stand rejected under 35 U.S.C. §103 as being unpatentable over Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia) in view of Hakimi, et al. (1991) J. Immunol. 147:1352-1359, Waldmann, et al. (1993) Blood 82:1701-1712 and Kreitman, et al. (1993) Bioconjugate Chem. 4:112-120. Applicants respectfully disagree with this rejection.

As discussed above, the combination of Waldmann (Ann. Oncol.), Waldmann (Imp. Adv. Oncol.) and Waldmann (Leukemia) fails to teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Hakimi, et al. discloses humanized anti-Tac, methods for making it and pharmacokinetics in monkeys. Hakimi, et al. does not teach or suggest conjugated antibodies or methods of human treatment using anti-Tac conjugates. Therefore, in combination with the other cited publications does not render the claimed invention obvious

because it does not add to the three Waldmann disclosures. Waldmann, et al. (Blood) discloses the same 5-15 mCi ^{90}Y doses disclosed in Waldmann (Ann. Oncol.), Waldmann (Imp. Adv. Oncol.) and Waldmann (Leukemia) and, like these publications, fails to teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Kreitman, et al. merely discloses cloning and expression of anti-Tac-Pseudomonas exotoxin fusions and toxicity studies but is silent on methods of human treatment using anti-Tac conjugates. Therefore, Kreitman, et al. does not add any teaching or suggestion to the insufficient prior art cited above. Thus, applicants urge that these references do not make out a *prima facie* case of obviousness. For these reasons, applicants respectfully request reconsideration and withdrawal of the § 103 rejection.

Claim 15 stands rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia) in view of Hakimi, et al., Waldmann, et al. (Blood) and Kreitman, et al. as applied to claims 1-14 and 16-25 above and in further view of Parenteau, et al. (1992) Transplantation 54:963-968. Applicants respectfully disagree with this rejection.

As discussed above, the combination of Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia) in view of Hakimi, et al., Waldmann, et al. (Blood) and Kreitman, et al. fails to teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to

nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. While the Parenteau, et al. publication discloses conjugated anti-Tac used for the prolongation of graft survival in conjunction with G-CSF treatment in primates, it does not teach or suggest a ratio of conjugated to nonconjugated anti-Tac as taught by the claimed invention. Further, there is certainly no teaching or suggestion to use soluble IL-2 receptor levels to determine the proper ratio of conjugated to nonconjugated anti-Tac to attain 25-75% saturation of IL-2 receptors for effective treatment of human disease. Parenteau, et al., when taken in combination with the cited art described above, does not render the claimed invention obvious because the combination of references does not teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Applicants therefore respectfully request reconsideration and withdrawal of the obviousness rejection.

Claims 25 and 26 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kozak, et al. (1986) Proc. Natl. Acad. Sci. USA 83:474-478, Diamantstein, et al. (1986) Immunol. Rev. pp. 5-27 in view of Order, et al. (1986) Intl. J. Radiat. Oncol. Biol. Phys. 12:277-281 or Wessels, et al. (1984) Med. Phys. 11:638-645. Applicants respectfully disagree with this rejection.

Applicants point out that claims 1-25 are pending and request clarification of this rejection.

Claim 25 is directed to pharmaceutical compositions which provides a ratio of conjugated to unconjugated anti-Tac such that the patient's sIL-2R levels is between 25 to 75% saturated. Kozak, et al. discloses methods of making effective anti-Tac conjugates, i.e., ^{212}Bi-labeled anti-Tac. However, there is no teaching or suggestion of any method of treatment or effective pharmaceutical composition disclosed. Kozak, et al. fails to teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. Diamantstein, et al. discloses the IL-2 receptor and unconjugated anti-Tac treatment of GVHD. Diamantstein lacks teaching or suggestion of (a) conjugate anti-Tac human treatment methods, (b) what doses of cytotoxic agent conjugates are administered, (c) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (d) the saturation level of IL-2 receptors required for effective treatment. Order, et al. discloses conjugated anti-ferritin (while the claimed invention is directed toward conjugated anti-Tac) in conjunction with the use of external radiation to increase antibody uptake. Order, et al. lacks teaching or suggestion of (a) conjugate anti-Tac human treatment methods, (b) what doses of cytotoxic agent conjugates are administered, (c) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (d) the saturation level of IL-2 receptors required for effective treatment.

Wessels, et al. discloses a theoretical study which actually teaches away from the claimed invention. The sentence spanning pages 641 and 642 states "As previously

stated, tumor associated antibodies labeled with radionuclides intended for a radiation therapy application require a high specific activity radiolabel..." (emphasis added). This statement tells the skilled artisan that the highest attainable specific activity, (ie., all conjugated anti-Tac with no unconjugated anti-Tac) is necessary for proper therapy. In contrast, the claimed invention teaches that a lower specific activity is, in fact, necessary to attain a therapeutic effect without excessive toxicity. The claimed invention teaches that the proper dosage is based upon a patient's soluble IL-2 receptor levels. In addition to teaching away from the claimed invention, Wessels, et al. lacks any teaching or suggestion of (a) a method of human treatment using conjugate anti-Tac therapy, (b) the doses of cytotoxic agent conjugates administered, (c) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (d) the saturation level of IL-2 receptors required for effective treatment. Applicants assert that there is no teaching or suggestion in the combination of the cited prior art which makes claim 25 obvious because the combination of cited art does not teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. In fact the cited prior art of Wessels, et al. teaches away from the claimed invention thus negating a determination of obviousness and supporting a determination of patentability of the claimed invention. Applicants, therefore, respectfully request reconsideration and withdrawal of the § 103 rejection.

Claims 1-25 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 13, 22 and 28 of co-pending application Serial No. 07/879,056 in view of Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia). Applicants respectfully traverse this rejection. Applicants urge that this rejection is premature. Upon allowance of the claimed invention and allowance of the claims of Serial No. 07/879,056, the filing of a terminal disclaimer to one of the inventions will be considered.

Claims 1-14 and 16-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia) in view of Hakimi, et al., Waldmann, et al. (Blood) and Kreitman, et al. for reasons of record and further in view of art known methods to monitor soluble IL-2 receptors, as evidenced by Rubin, et al. (1990) Ann. Int. Med. 113:619-627. And claim 15 stands rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol.) or Waldmann (Imp. Adv. Oncol.) or Waldmann (Leukemia) in view of Hakimi, et al., Waldmann, et al. (Blood) Kreitman, et al. and Rubin, et al. as applied to claims 1-14 and 16-25 above and in further view of Parenteau, et al. Applicants respectfully disagree with these rejections.

As stated above, the combination of Waldmann (Ann. Oncol.), Waldmann (Imp. Adv. Oncol.), Waldmann (Leukemia), Hakimi, et al., Waldmann (Blood), Kreitman et al., and Parenteau, et al. does not teach or suggest the present invention because the

combination of these references fails to teach or suggest (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. This is a fact to which the Examiner agrees as evidences on page 8, fifth paragraph of the November 26, 1997 Official Action: "[t]he prior art of record does not disclose generating effective doses that achieve 25-75% saturation of IL-2 receptors per se." Applicants agree with this fact.

Rubin, et al. discloses potential clinical applications of the soluble IL-2 receptor. The applications described in Rubin, et al. are diagnostic in nature and relate to measuring disease activity, response to therapy, and, in some cases, prognosis in conditions associated with T- or B-cell immune activation. There is no teaching or suggestion that sIL-2R levels can be used to calculate effective dosing for the treatment of disease. Further, there is no teaching or suggestion as to (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required for effective treatment. As the Examiner stated, there is no teaching or suggestion in the cited prior art of an effective treatment dosage according to the claimed invention. When the prior art of record is combined with Rubin et al., there still is no teaching or suggestion of (a) what doses of cytotoxic agent conjugates are administered, (b) the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered, and (c) the saturation level of IL-2 receptors required

for effective treatment. Applicants therefore respectfully request reconsideration and withdrawal of the §103 rejections.

Claims 1-18 and 24-25 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Examiner contends that the recitation "said ratio based upon soluble IL-2 receptor levels, such that 25 to 75% saturation of total IL-2 receptors is provided" and "wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75% saturation of IL-2 receptors by said cytotoxin conjugate" make the claims indefinite because it is unclear whether these limitations are properties of effective dosages already claimed or whether these limitations are drawn to discrete and additional method steps. Applicants respectfully disagree with this rejection.

The limitations in question are an important aspect of determining and thus providing an effective dosage. In order for a dosage to be effective, IL-2 receptor saturation of between 25% and 75% is considered optimal. This level of saturation is attained by following the disclosure of the claimed invention. First, the practitioner determines a patient's soluble IL-2R level. Second, the proper dose is determined according to the following guidelines:

sIL-2R level	Total amount of anti-Tac
less than 2,000 units/ml	2 mg
2,000 - 10,000 units/ml	5 mg
10,000 - 50,000 units/ml	10 mg
more than 50,000 units/ml	20 mg

Third, the dose is administered to the patient. This procedure is outlined in Example 16 of the instant specification. Applicants assert that in light of the above remarks, claims are definite and reconsideration and withdrawal of the §112 rejection is respectfully requested.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4003US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or

credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4003US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: March 23, 1998

By: _____
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